PM Toxicology: Latest Findings and EPRI's New Research Initiatives

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- Evidence from Toxicology: PM Sources
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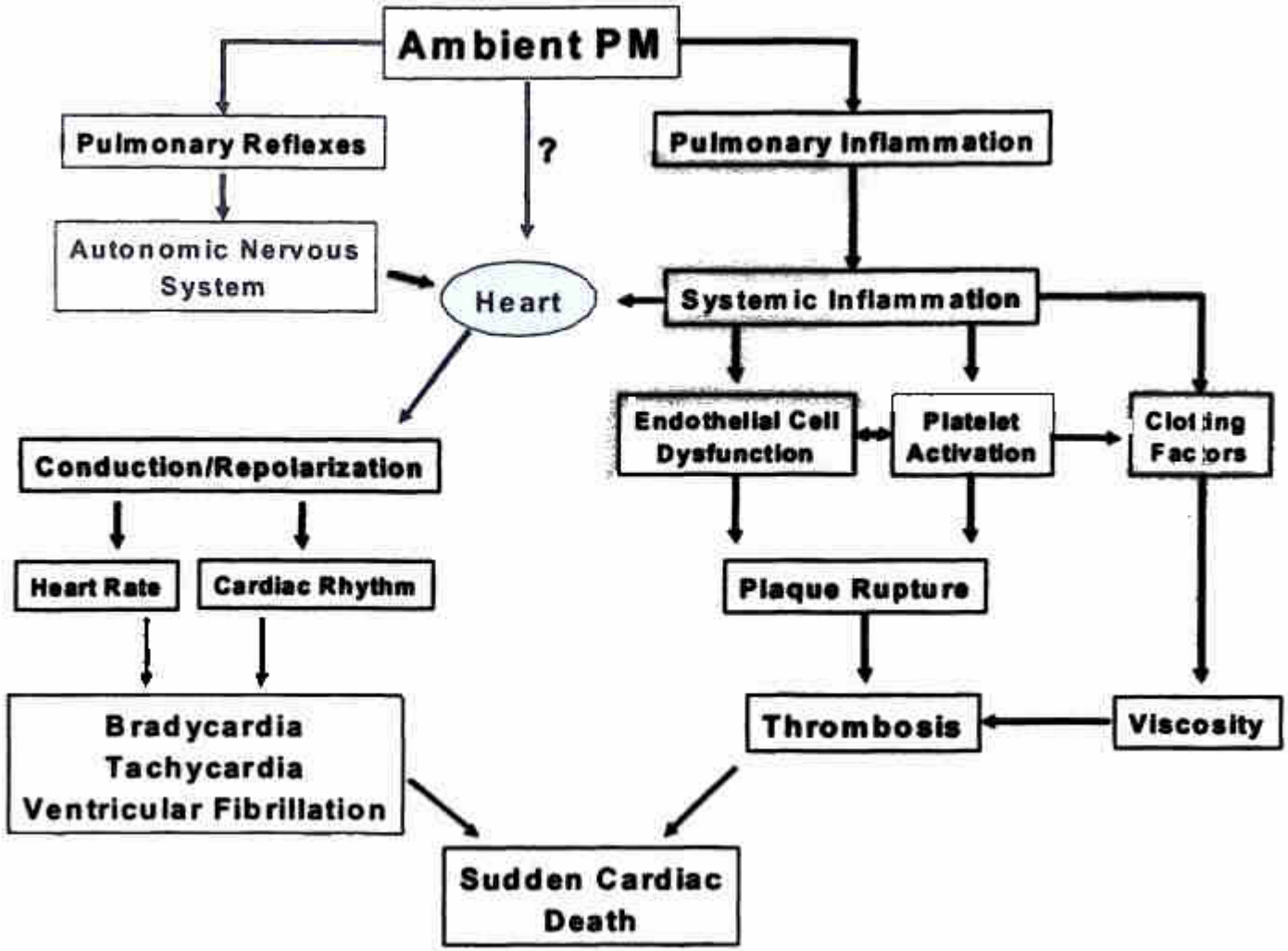
- EPRI Toxicology Projects:
  - TERESA (Toxicological Evaluation of Realistic Emissions of Source Aerosols)
  - Characteristics of Premature Mortality in Mice: Application to PM

Introduction

Toxicological studies can play a key role in PM health research by answering the following three questions :

- What component(s) cause health effects?
- What are the biologic mechanisms?
- How might susceptible subpopulations be affected?

Possible Biological Mechanisms of PM-Induced Sudden Cardiac Death



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Susceptible Subpopulations

- Humans:
  - Chronic obstructive pulmonary disease (COPD)
  - Myocardial infarction (MI)
  - Asthma
  - Diabetes
- Animal models:
  - Aged animals.
  - Spontaneously hypertensive rats.
  - Chronic bronchitis.
  - Rats and dogs with surgically-induced coronary heart disease.
  - Rats with cardiopulmonary disease.
  - “Asthmatic” mice.
  - Certain types of “knockout” animals.

Hypothesized Agents Causing Adverse Health Effects

- PM mass concentration (fine, coarse)
- Ultrafine particles
- Metals (water-soluble, transition)
- Acids
- Elemental carbon
- Organic carbon
- Biological agents (pollen, mold, etc.)
- Sulfates
- Nitrates
- Gas-phase pollutants (CO, NO_2, SO_2, ozone, hydrocarbons)
- Peroxides and other reactive species

Evidence from Toxicology: PM Components

- **Metals**: Much research with ROFA. Substantive evidence for a role for metals, esp. V, Fe, Ni. Findings suggest that soluble metals may be more important than insoluble metals. Recent findings suggest a role for Si.
- **Acid aerosols**: Some strong acids (eg. H_2SO_4) can cause pulmonary effects at high concentrations.
- **Sulfates/nitrates**: Little effect in animals and human volunteers.
- **Ultrafines**: Evidence is unclear.
- **Bioaerosols**: Generally considered to be more of an issue with larger particles, but now gaining some attention with respect to fragments of allergens in $PM_{2.5}$.
- **Organic compounds**: Comprise 10-60% of PM dry mass, but very little is known about health effects.

Evidence from Toxicology: PM Sources Residual Oil Fly Ash (ROFA)

- Enriched in transition metals, used extensively to test the "metals hypothesis".
- Negligible source of human exposure.
- Heavily studied: multiple endpoints evaluated and responses observed.
- Recent studies: increased transcription factor production in perfused lung (Samet et al., 2002), changes in gene expression (Nadadur and Kodavanti, 2002), decreased heart rate and temperature, and increased arrhythmias in rats (Campen et al., 2002).

Evidence from Toxicology: PM Sources Wood Smoke

- Residential wood smoke accounts for a significant proportion of ambient PM in some areas, eg. in Portland, OR, 51% of respirable PM originated from residential wood combustion sources (Cooper, 1980), similar findings in other parts of the Northwest. In Atlanta, ARIES source allocation results show wood burning is largest contributor to $PM_{2.5}$ in winter, and >50% of OC.
- Wood smoke largely studied in terms of its constituents rather than as a mixture, but some health effects have been demonstrated:
  - Decreased ventilatory frequency,CO_2 response (Wong et al., 1984).
  - Increased microvascular permeability, pulmonary edema (Nieman et al., 1988).
  - Rats exposed to 750 $\mu g/m^3$ wood smoke (mass median diameter = 0.16 μm) for 1 hr/day for 4 days demonstrated compromised resistance well after exposures ceased, also decreased phagocytic activity and superoxide production (Zelikoff et al., 1995).
  - Rats exposed to 1 or 10 mg/m^3 wood smoke PM for 3 hours/day, 5 days/week for 4 or 12 weeks showed minor but significant changes in pulmonary resistance, CO-diffusing capacity, mild chronic inflammation, squamous cell metaplasia in larynx (Tesfaigzi et al., 2002).

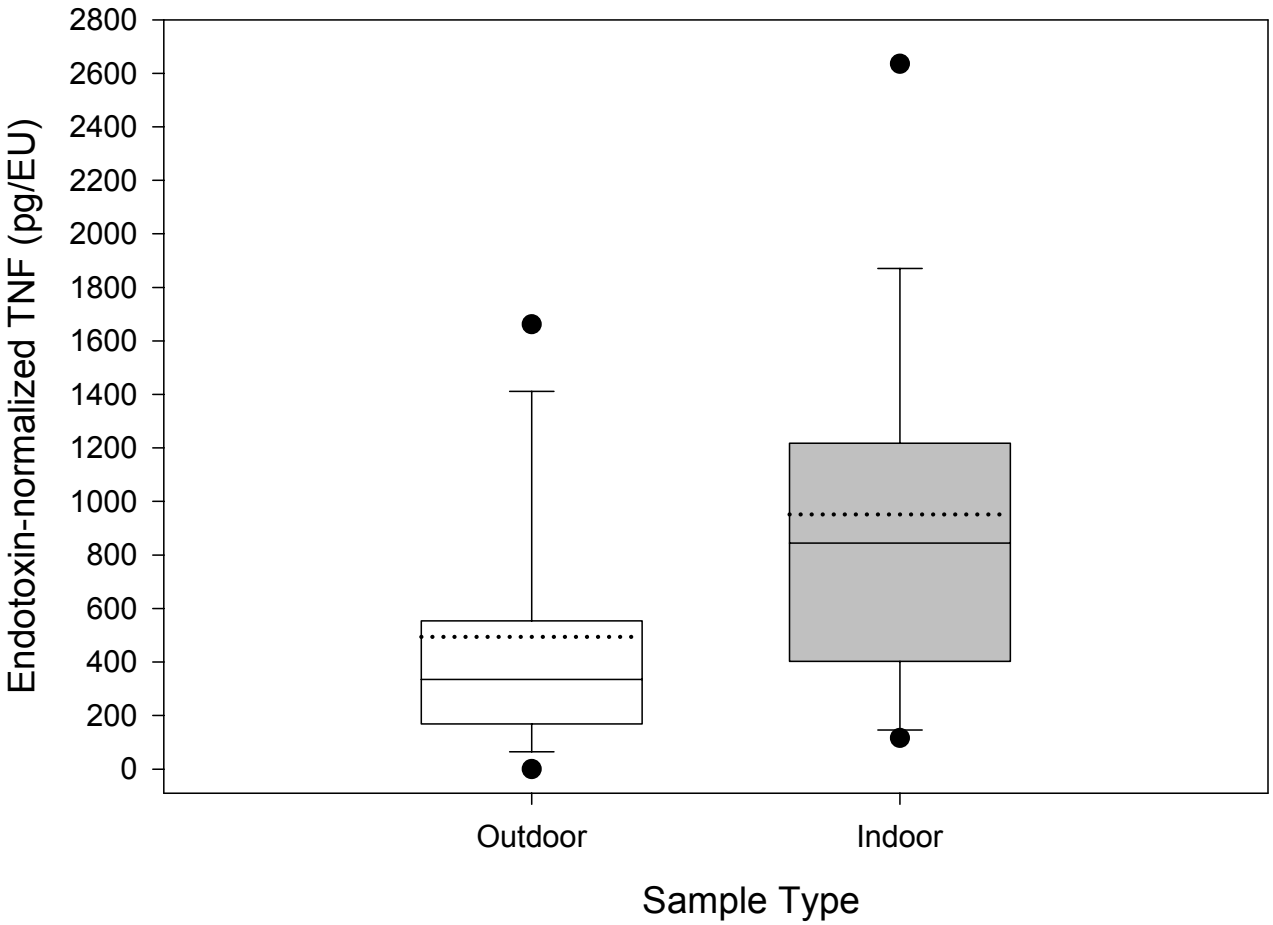
Evidence from Toxicology: PM Sources Mobile Sources

- Few inhalation studies using whole emissions.
- Most evidence for exacerbation of allergic responses, immune function compromise, especially with diesel exhaust particles.
- Diesel exhaust particles (intravenous): water-soluble fraction induced arrhythmias and death by AV block (Minami et al., 1999).
- Traffic PM extracted into different fractions: organic acids and highly polar compounds: possible adjuvants? Increased IL-5, IgE, eosinophils, bronchial reactivity (Fernvik et al., 2002).
- NERC diesel emissions results being analyzed; preliminary results indicate only very subtle effects over a 6-month exposure period.

Evidence from Toxicology: PM Sources Concentrated Ambient Particles (CAPs)

- Concentrators increase PM levels by a factor of 30 to 100, enabling exposure to “real life” particles at concentrations more likely to induce effects over a shorter exposure period.
- Concentrated ambient particles (CAPs) vary day-to-day and place-to-place, and can be thoroughly characterized to allow consideration of specific components in analyses.
- Selected recent findings from CAPs studies:
  - Decreased heart rate and blood pressure in spontaneously hypertensive rats (Cheng et al., 2002).
  - Decreased pulmonary artery lumen/wall ratio in rats (ie. vasoconstriction) associated with $PM_{2.5}$, Si, Pb, SO_4, EC, OC, though only Si remained significant in multivariate models (Batalha et al., 2002).
  - Decreased HRV, HR, T wave alternans, changes in breathing pattern in dogs (Godleski et al., 2000).

Evidence from Toxicology: PM Sources Indoor PM



(Long et al., 2001)

Evidence from Toxicology: PM Sources Coal Combustion

- All studies have been conducted using primary coal fly ash (CFA), not secondary particles. Typically, ESPs remove 99+% of PM from stack emissions, making the relevance of these exposure conditions unclear.
- Mostly intratracheal instillation studies, few inhalation studies.
- Early work by Alarie et al. (1975) and MacFarland et al. (1971) in rodents and monkeys demonstrated no unique biological effects from CFA exposure.
- Instilled CFA reported to cause reductions in antibody-forming cells in rats (Dogra et al., 1995), reductions in total and vital capacity in guinea pigs (Chen et al., 1990), and changes in lung histopathology in hamsters (Wehrer et al., 1979, 1980).
- *In vitro*: acellular OH generation and cytotoxicity in rat epithelial cells (van Maaenen et al., 1999), decreased phagocytic activity in mouse alveolar macrophages (Fisher and Wilson, 1980).
- Little effect on DNA (Prahalad et al., 2000, 2001); effect seemed to be mediated primarily by V and Ni.

Toxicological Evaluation of Realistic Emissions of Source Aerosols (TERESA)

Overview/Features

•Evaluate toxicity of *secondary* coal combustion emissions at multiple power plants in the U.S.

•Conduct extensive exposure characterization.

•Assess multiple toxicological endpoints in normal and susceptible rats.

•Determine relative toxicity of coal combustion and mobile source emissions.

•Determine the effect of atmospheric conditions on secondary PM formation/toxicity.

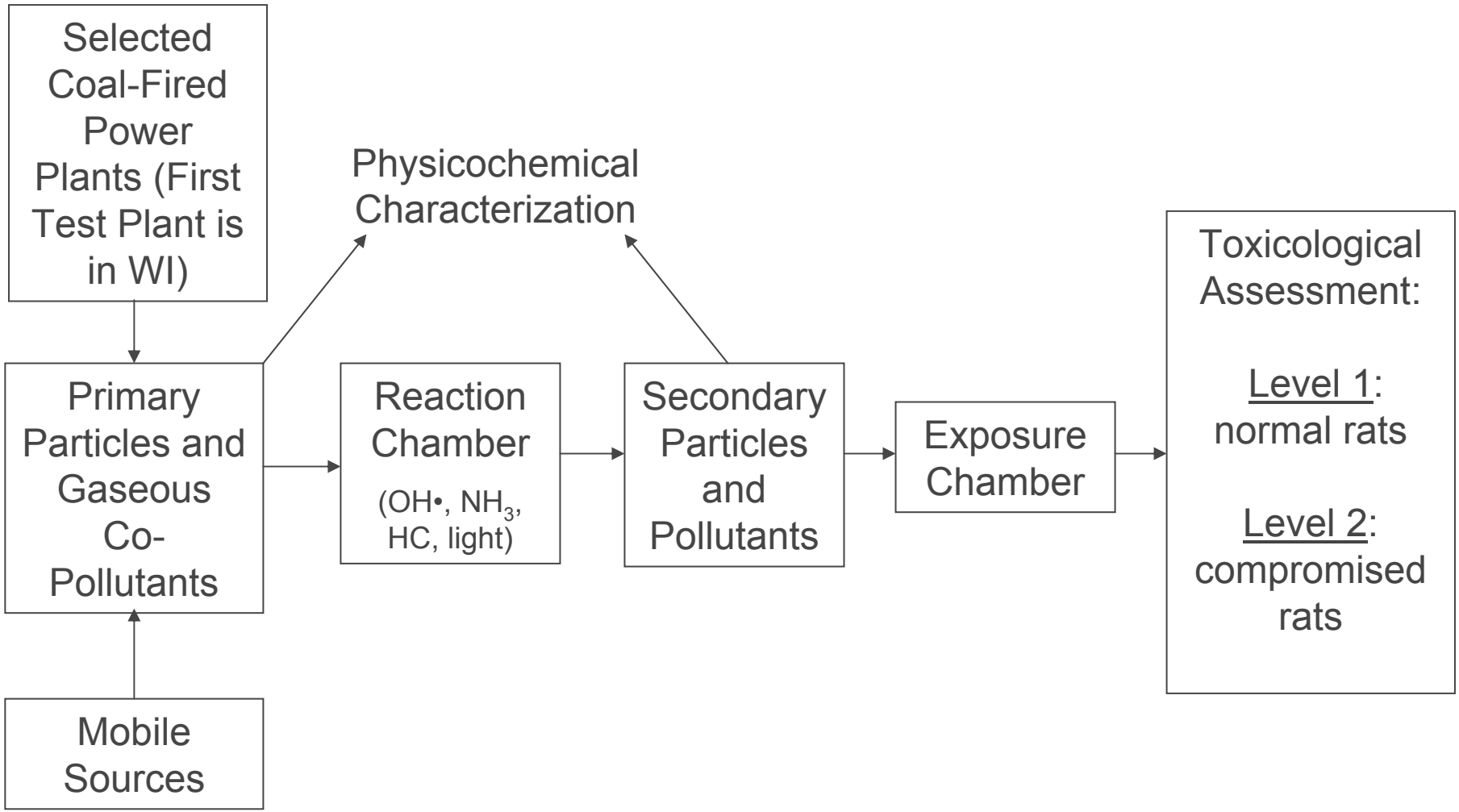
TERESA: Motivation for Research

- The toxicity of primary coal combustion emissions (coal fly ash) has been assessed (for some endpoints) – but there is no information on the toxicity of *secondary* particles formed.
- Also, direct inhalation exposures to actual plant emissions have not been done. Emissions from pilot combustors may differ from full-scale plants due to differences in surface area/volume ratios and therefore time-temperature histories.

TERESA: Project Objectives

1. Investigate the toxicity of coal combustion emissions by utilizing realistic exposures that consider secondary chemistry.
2. Investigate the effect of atmospheric conditions and aging on secondary particle formation and toxicity.
3. Provide insight into toxicological mechanisms of PM-induced effects, particularly as they relate to susceptible subpopulations.
4. Compare the toxicity of coal combustion emissions with secondary mobile source emissions and ambient PM.

TERESA: Study Design



TERESA: Atmospheric Simulation

- Continuous sample from stack to mobile chemical laboratory on the ground.
- Cooled and diluted emissions introduced into a reaction chamber in the mobile lab (currently under construction).
- Atmospheric components introduced:
  - OH• to enhance oxidation reactions
  - $NH_{3(gas)}$ to partially neutralize acidic sulfate particle strong acidity
  - Hydrocarbons (artificial or from ambient air) to allow conversion of biogenic VOCs to secondary organic aerosol
  - Inert particles to serve as seed nuclei
  - Spectrum- and intensity-controlled light
- Control of temperature and RH.

TERESA: Exposure Characterization

- PM mass, number, size distribution (including ultrafines)
- Sulfate, nitrate
- EC/OC
- Ammonium
- Metals (total and water-soluble)
- Selected organics (eg. PAHs)
- Gaseous pollutants: CO, NO_2, SO_2, ozone, NH_3

TERESA: Toxicological Assessment

- Conducted in separate mobile toxicological laboratory.
- 4-hour exposures, with 1-hour baseline and recovery periods (room air).
- Six scenarios for power plant emissions:
  1. Sham exposure (air only)
  2. Primary emissions
  3. Typical aged plume (oxidation atmosphere)
  4. Typical aged plume (oxidation atmosphere) plus ammonia
  5. Typical aged plume (oxidation atmosphere) plus VOCs
  6. Control (atmospheric components only, no emissions)
- Same scenarios for mobile source emissions.
- Draw on existing data to perform comparative toxicity assessment of CAPs.

TERESA: Toxicological Assessment

Stage I Assessment (normal rats):

- Pulmonary function/breathing pattern
- *In vivo* oxidative stress via chemiluminescence
- Blood cytology (CBC/differential)
- Bronchoalveolar lavage (LDH, βNAG, total protein)
- Pulmonary histopathology

Stage II Assessment (rat MI model; Wellenius *et al*., 2002):

- Telemetry: cardiac function (ECG, HR, HRV), blood pressure, core body temperature
- Blood chemistry (endothelin-1, CRP, IL-1, IL-6, TNFα)
- Pulmonary function/breathing pattern

TERESA: Expected Outcomes

Data from the project will indicate:

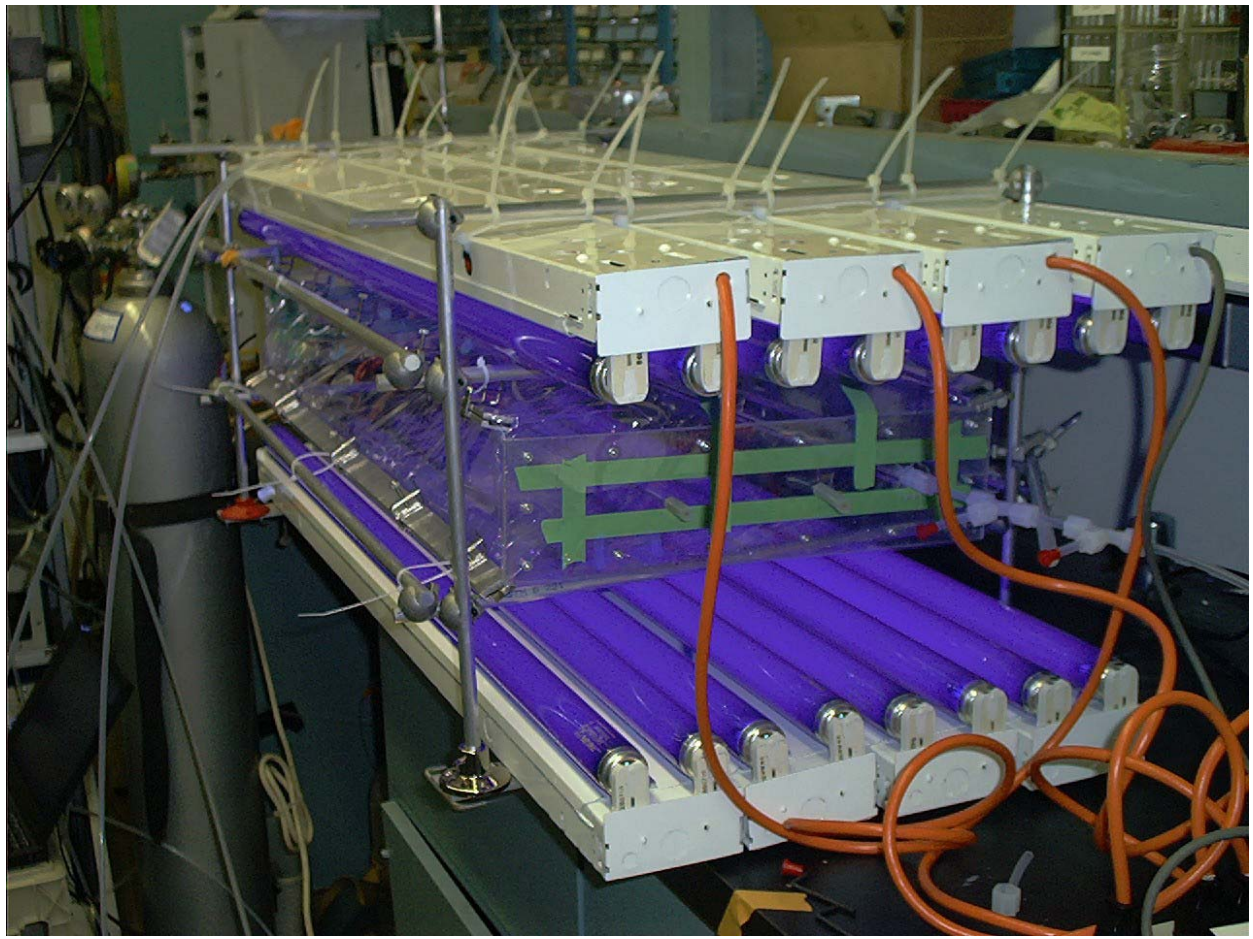
- For the first time, the potential for health effects from exposure to realistic coal-fired power plant emissions.
- The effect of atmospheric conditions on the formation and toxicity of secondary particles from coal combustion and mobile sources.
- How PM derived from coal-fired power plants, mobile sources, and the ambient environment compare in terms of health effects.
- The components of PM most likely to induce effects.
- Potential biological mechanisms of PM-induced effects.
- How sensitive individuals might be affected by PM exposure.

TERESA: Status

- Design of sampling system, photochemical chamber, mobile laboratories is underway.
- Laboratory testing of a prototype photochemical chamber with SO_2 and NO_x has begun.
- Fieldwork in Wisconsin scheduled for summer 2003.

Prototype Photochemical Chamber

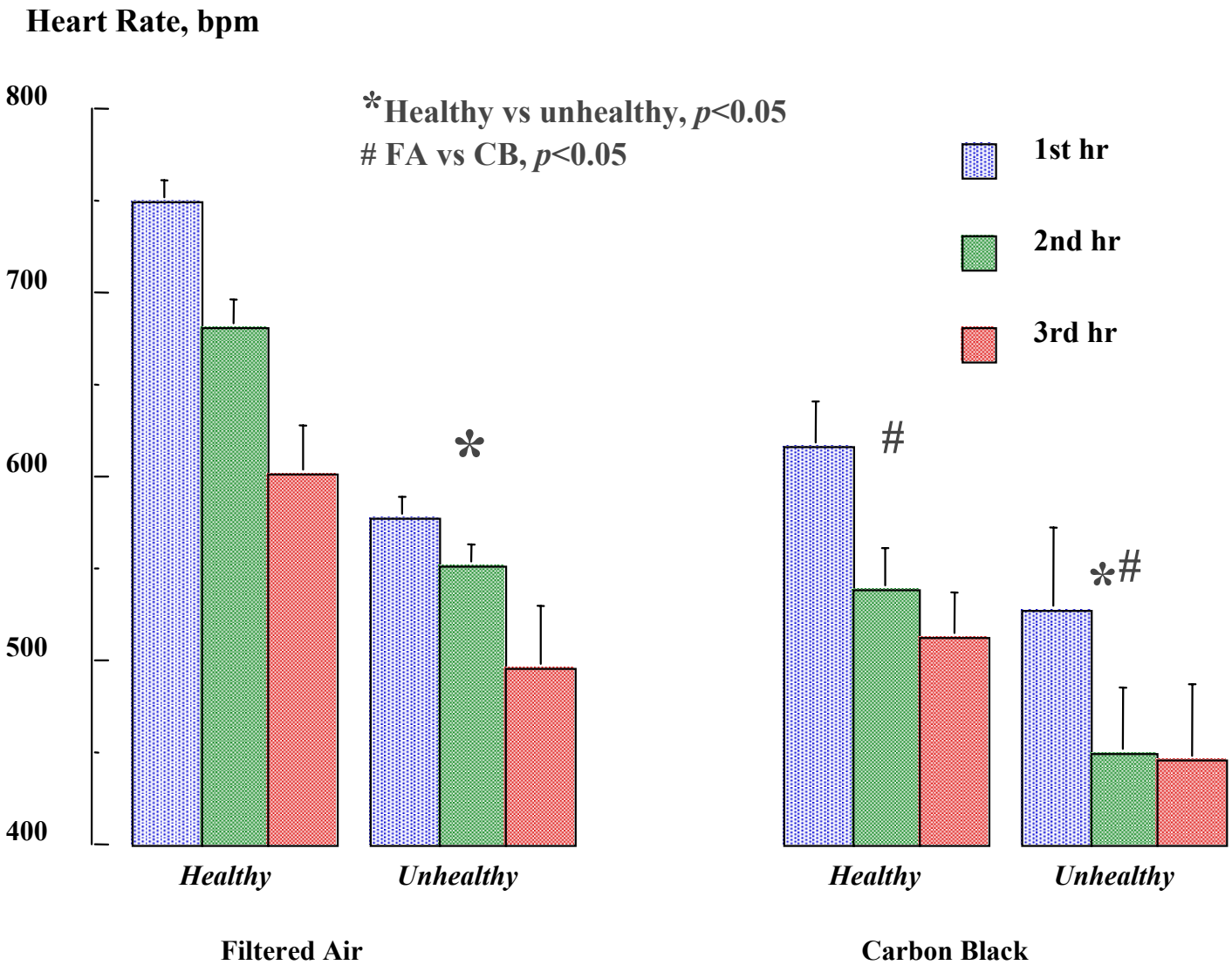
- 3’ x 1.5 ‘ x 6”
- Approx. 45 L
- Walls: 2 MIL FEP Teflon film
- Lights: 16 X 40 W, T12 Black Lights
- OH generation:
  - HONO photolysis
  - Alkene (ethene) + O_3
  - H_2O_2 photolysis
  - HCHO photolysis



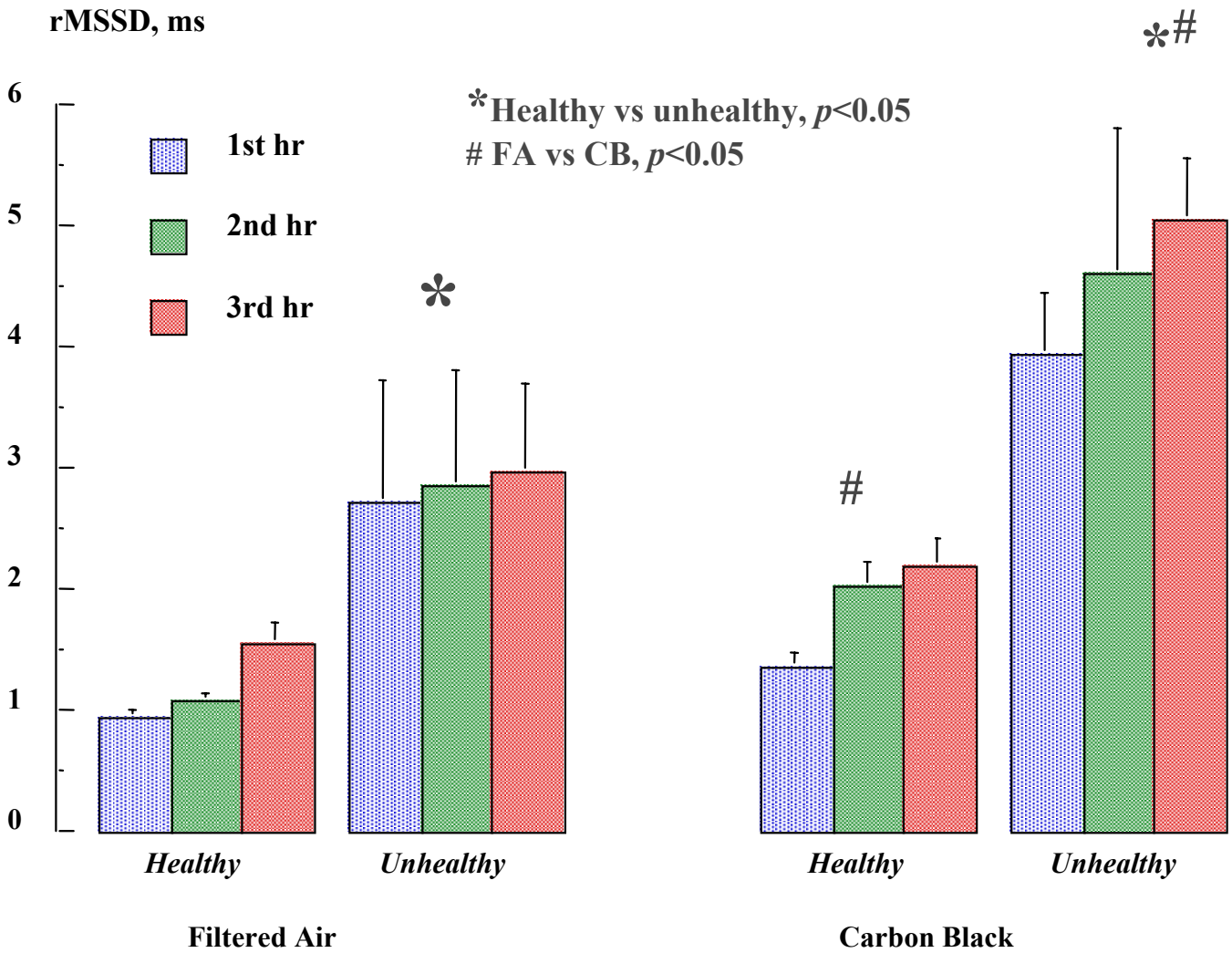
Characteristics of Premature Mortality in Mice: Application to PM

- Work being carried out by Tankersley et al. (Johns Hopkins) in aged mice.
- Previous work showed that decreases in heart rate (bradycardia) and the loss of circadian rhythm in body temperature represent the most proximal signals of imminent death.
- Current work designed to answer two questions:
  1. Does PM exposure increase the risk of premature mortality in aged animals that are nearing death?
  2. If so, by what mechanism(s) is this advancement of death occurring?

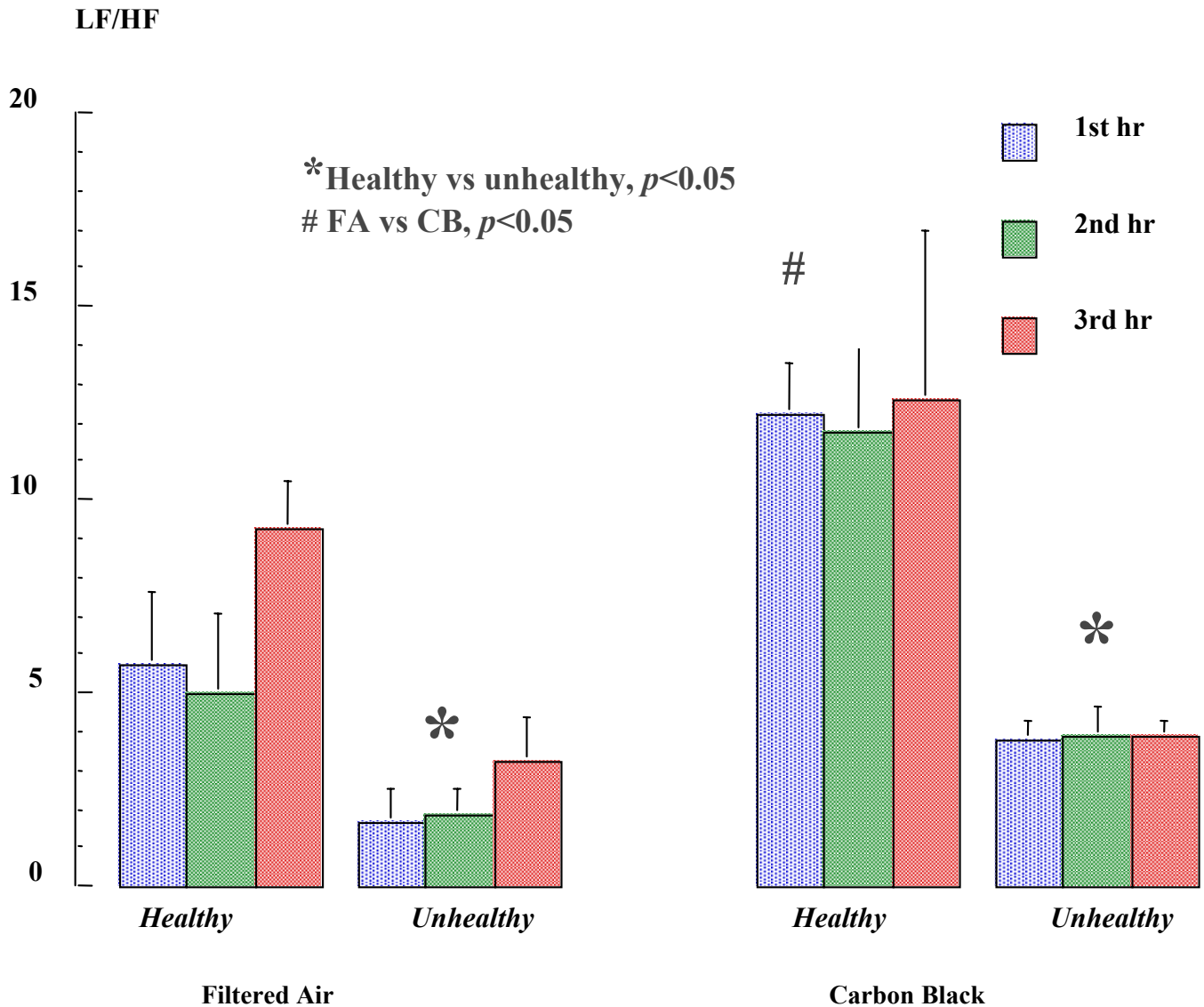
Heart Rate in Healthy and Unhealthy AKR Mice Exposed to Filtered Air (FA) or Carbon Black (CB)



rMSSD in Healthy and Unhealthy AKR Mice Exposed to Filtered Air (FA) or Carbon Black (CB)



LF/HF in Healthy and Unhealthy AKR Mice Exposed to Filtered Air (FA) or Carbon Black (CB)



Characteristics of Premature Mortality in Mice: Application to PM (Tankersley et al.)

- PM exposure acutely exacerbates bradycardia in aged animals nearing death.
- In healthy ("young") mice, exposure to PM appears to lead to increased sympathetic nervous system activity consistent with a generalized stress response.
- In unhealthy ("aged") mice, PM exposure seems to cause a greater parasympathetic tone and deficiencies in cardiac sympathetic tone, leading to bradycardia.

- **Results challenge the current hypothesis that PM causes sympathetic activation leading to tachyarrhythmias/fibrillation and death.**
- **Hypothesis**: greater numbers of bradycardic arrhythmias in aged mice close to death increase the risk of acute mortality from PM exposure.